VASCULAR COMPLICATIONS OF DIABETES MELLITUS*

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THE generally accepted definition of diabetes mellitus as an impairment of carbohydrate metabolism due to *insulin insufficiency* is inadequate. It should include the associated phenomenon of *premature vascular degeneration* as an integral part of the clinical syndrome.[1] The *diagnosis* of diabetes mellitus cannot be limited merely to a few classical symptoms fortified by *chemical* determinations of urine and blood sugar but must include *clinical* recognition of the generalized systemic manifestations of the disease.

A number of different procedures are responsible for the induction of diabetes both experimentally and clinically, through the production of relative or absolute insulin deficiency, e.g.:

1. An absolute decrease in available insulin (severe intrinsic pancreatic disease and total pancreatectomy).

2. Increased need for insulin due to its increased utilization (overfeeding, obesity and hyperthyroidism).

3. An increase in the rate of insulin destruction (infection and trauma).

4. A decrease in the responsiveness of the enzyme systems affected by insulin (endocrine factors such as purified growth hormone, crude anterior pituitary extract, adrenal cortical steroids, and ACTH, and liver disease).

5. The production of insulin antagonists or neutralizing agents.

The multiplicity of possible etiologic mechanisms justifies classification of diabetes mellitus as a symptom complex and not a specific disease entity except for the relatively infrequent instances of pancreatic desruction or extirpation and adrenal cortical hyperfunction.

Whatever etiologic factors finally result in the manifestation of hyperglycemia and glycosuria, they must be operative in the pathogenesis

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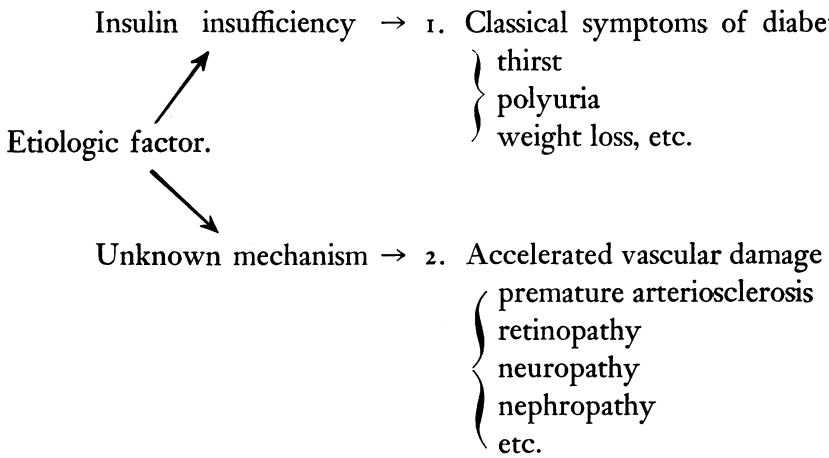
of diabetes *long before* a disturbance of carbohydrate metabolism becomes obvious. The bearing of an excessively large infant may portend the future onset of diabetes in the mother. So-called "diabetic complications" are often fully developed by the time glycosuria or the classical symptoms of thirst and polyuria are noted. Although this is generally true of patients beyond middle age, even young adults may present evidences of premature, accelerated vascular damage such as diabetic retinopathy, etc. without hyperglycemia and little or no impairment of glucose tolerance.[2] This is further substantiated by Colwell's[3] ingenious calculations that diabetes has progressed through half its course by the time clinical recognition is effected.

From the standpoint of dynamics, diabetes mellitus may be conceived as comprising two distinct groups of manifestations developing at different rates of speed.



Observation of totally depancreatized human beings over a period of the next twenty years will prove whether simple insufficiency of insulin alone can be responsible for the degenerative changes. In the average case of diabetes mellitus this relationship is obscured by possibility of degenerative or catabolic effects arising *independently* from as yet unknown etiologic factors. Arteriosclerosis, hypertension and diabetes mellitus may have a common origin, the causative agent producing insulin insufficiency only incidentally and only in susceptible individuals.

The primary appearance of typical "diabetic" symptoms which characterize the onset in all juvenile, most young adult and one third of the

VASCULAR DAMAGE IN TWO HUNDRED PATIENTS

		At the Time of Onset of Retinal Hemorrhage				
Age of Onset of Diabetes	*No. of Patients*	*Average Duration of Diabetes, Yrs.*	*Patients with Hypertension*		*Patients with Albuminuria*	
			No.	*%*	*No.*	*%*
0-19	55	13.0	27	49.1	24	43.6
20-29	21	13.3	9	42.9	10	47.6
30-39	45	13.0	21	46.7	23	51.1
40-49	79	10.0	37	46.8	48	60.8
Total	200		94		105	

older adult patients overshadows the insidious, slowly progressive secondary degenerative changes for a number of years. With *increasing duration* of diabetes, however, the latter break through the unrecognized subclinical stage finally to produce a variety of clinical manifestations, formerly regarded as "complications." An average of about thirteen years duration of diabetes has been noted as the time of the first appearance of these secondary associated phenomena.[1]

The disparity of primary and secondary manifestations at the *onset* and their fusion later in *young* diabetic patients may be depicted as follows:

	Onset	*13 to 20 years later*
Symptoms of Insulin Insufficiency	+	+
Accelerated Vascular Damage	o	+

The course of degeneration in juvenile diabetes varied widely, with no apparent relation to the amount of insulin required or to the ability to control glycosuria. Rapidly progressive lesions were noted in some young patients whose glycosuria was marked and almost constant as well as in some in whom glycosuria was rare and mild. Inexplicably, several juvenile diabetics, displaying persistent glycosuria, presented only minimal lesions of vascular damage by the twenty-fifth year. Their fate was no worse than that of the youngsters whose observance of diet and management with insulin afforded no difficulty in avoiding appreciable glycosuria. Some factor as yet unknown must be invoked to explain the

inherent resistance of the vascular systems of these two differently treated groups of young patients whose lesions progressed relatively slowly.

"The prognosis of diabetes in childhood—taking a long view—is in spite of the progress of dietary and insulin treatment more adverse than had originally been expected."[4] My observations revealed diabetic retinopathy in every instance within a twenty-five year duration of the disease.[1] This has now been confirmed by others.[5, 6] White,[5] in a survey of 200 juvenile patients surviving 20 years of diabetes, found vascular damage in 92 per cent, while Chute,[6] in a smaller group with similar duration, noted it in 85 per cent. The most dismal report, that of Fanconi's Clinic,[7] concludes that "16 years after the commencement of diabetes no patient is free from nephropathy; after 21 years not a single patient is still alive." A tour of the continent of Europe failed to reveal a single case entitled to a victory medal for having lived with diabetes for twenty-five years without evidences of vascular damage, according to Joslin.[8]

Classical "diabetic" symptoms *cannot* be elicited in *over fifty per cent* of middle aged and elderly patients when glycosuria is first discovered.[9] At this time many of the asymptomatic patients and about one-fifth of the group with "diabetic" symptoms already present evidences of accelerated vascular degeneration.[1] In fact, the degenerative phenomena may precede the appearance of hyperglycemia and glycosuria.

The three types of *onset* of diabetes in patients *beyond middle age* may be depicted in contrast with that of younger individuals, as follows:

	Onset		
Symptoms of Insulin Insufficiency.....	o	+	+
Accelerated Vascular Damage	+	+	o

Such differences in the clinical course account for the high incidence of unrecognized diabetes and the finding of a "casual onset" or an "onset with complications" in *66 per cent* of all patients.[9] Only *34 per cent* presented themselves because of "diabetic" symptoms.

The incidence of premature arteriosclerosis in the adult as measured by retinopathy, hypertension and albuminuria appears to be identical with that in the juvenile diabetic. Here, too, the earliest retinal lesions were noted about thirteen years after onset of diabetes, and associated with hypertension and albuminuria in about 50 per cent of patients.[1] An

apparent acceleration of the lesions was typical of the mild cases in this older age group, because of the insidious undramatic onset of diabetes so that duration of the disease could not be determined accurately. The incidence of fatal coronary disease in diabetes is *twice* that of non-diabetic males and *triple* that of non-diabetic females.[10] Therefore, suspicion of asymptomatic diabetes should be aroused in every case of *coronary artery disease*, particularly in *women* since they normally present an incidence of such cardiovascular involvement only about half as frequently as men. The diabetic predisposition to *peripheral vascular disease* is even more striking. Bell[11] claims that on the basis of arteriosclerosis alone, *gangrene* develops nearly *forty* times more frequently in diabetic than in non-diabetic individuals. As with coronary artery disease, diabetes obliterates the normal sex differences of masculine predominance in peripheral arteriosclerosis, the frequency in both sexes being equal when diabetes is present. Mirsky[12] noted a similar equalization of the sexes with respect to the incidence of diabetic neuropathy, impairment of vibratory sense perception appearing soon after the onset of diabetes and increasing strikingly after 13 years duration of the disease. the same period of time previously observed for the average onset of early retinopathy. As in retinal damage, the neurologic disturbances could not be correlated with the age of the patient, the "severity" of diabetes or the level of "control" of glycosuria.

Nerve tissue, which also includes the retina, represents the most sensitive indicator of vascular damage, with minute lesions often producing major disturbances. These degenerative manifestations are so varied and so protean in character that diabetes now surpasses syphilis as "the Great Imitator." Involvement of the nutrient vessels, the vasa nervosum, occurs in both central and peripheral portions of the nervous system. In addition to the well known diabetic "complications" of peripheral neuropathy increasing recognition is being given to similar vascular lesions of the brain stem, mid-brain, cerebrum, spinal cord and autonomic nervous system. The classic syndrome of occlusion of the posterior inferior cerebellar artery is characteristic of diabetes. Intramedullary hemorrhage accounts for the transient external ocular muscle paralysis which Weinstein and I[13] reported as being more frequently associated with diabetes than with lues. Pupillary abnormalities, including Argyll Robertson pupils, are also indicative of mesencephalic involvement on a diabetic vascular basis. Vascular myelopathy may lead to the development of

diabetic pseudotabes, Charcot arthropathy, impotence, neurogenic bladder and bowel disturbances, trophic skin changes and ulcerations, muscle atrophy due to anterior horn degeneration, etc. Disturbances in autonomic nerve supply plus the added insult of peripheral neuropathy jeopardize the diabetic patients already suffering from circulatory impairment of the extremities. Unfortunately the vascular lesions in both nerve and retinal tissue, being irreversible, do not respond to the administration of vitamin or protein supplements or to treatment of the underlying diabetic state itself. Therapeutic failure has followed the use in large doses of all the components of the vitamin B complex, including B_1 and B_{12} and the various preparations purporting to contain vitamin P, such as rutin and hesperidin.[14] In fact recent evidence indicates that none of the flavonoid substances including rutin are even absorbed in any appreciable amounts.[15]

Accelerated vascular damage which is an associated phenomenon and not a complication of diabetes appears to be related primarily to the duration of the disease; its course up to the present time has not been altered significantly by the use of insulin, the type of diet or the level of control of glycosuria and hyperglycemia. The subject of arteriosclerosis in diabetes mellitus has been limited to consideration of late complications such as gangrene, peripheral vascular and coronary artery disease. The existence of earlier generalized lesions is now generally recognized and the physician must broaden the scope of his examination of diabetic patients, searching persistently for evidences of incipient vascular damage. The usual analysis of urine and blood for glucose and the traditional catechism regarding the diet are inadequate for a complete evaluation of the patient's condition. Careful scrutiny of the fundi for early retinal hemorrhages, examination of the urine for albumin and casts, measurement of vibratory sense perception, and determination of the blood pressure on every visit with the diabetic patient will reveal an astonishing incidence of abnormalities in these areas. Thereby will be revealed a common paradox wherein the so-called "mild diabetic" patient may be found manifesting "severe complications," and conversely the so-called "severe diabetic" patient at times displaying only "mild vascular complications." However, regardless of the severity of the condition or its treatment, accelerated vascular damage is the inevitable fate of all patients suffering from diabetes mellitus at the present time.

[*REFERENCES ON NEXT PAGE*]

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